

Appendix
Copy of Goodman & Gilman's
The Pharmacological Basis of Therapeutics
Pages 1364 - 1368

Best Available Copy

GOODMAN & GILMAN's The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

McGraw-Hill

HEALTH PROFESSIONS DIVISION

New York St. Louis San Francisco Auckland Bogotá Caracas Lisbon London Madrid
Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

McGraw-Hill

A Division of The McGraw-Hill Companies



Best Available Copy

Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. 9/e

Copyright © 1996, 1990, 1985, 1980, 1975, 1970, 1965, 1955, 1941 by The McGraw-Hill Companies, Inc. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

34567890 DOWDOW 9

ISBN 0-07-026266-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and Peter McCurdy; the production supervisors were Robert Laffler and Clare Stanley, and the cover designer was Marsha Cohen/Paralellogram. The index was prepared by Irving Condé Tullar.
R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*. —9th ed. / Joel G. Hardman, Alfred Goodman Gilman, Lee E. Limbird.

p. cm.

Includes bibliographical references and index.

ISBN 0-07-026266-7 (hardcover)

1. Pharmacology. 2. Chemotherapy. I. Goodman, Louis Sanford. II. Gilman, Alfred.
III. Hardman, Joel G. IV. Gilman, Alfred Goodman. V. Limbird, Lee E.
[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 1995]

RM300.G644 1995

615'.7—dc20

DNLM/DLC

for Library of Congress

95-36658

Table 55-1

Properties of the Protein Hormones of the Human Adenohypophysis and Placenta

HORMONE	APPROXIMATE MOLECULAR MASS, Da	PEPTIDE CHAINS	AMINO ACID RESIDUES	CARBO- HYDRATE	COMMENTS
<i>Somatotropic Hormones</i>					
Growth hormone (GH)	22,000	1	191	0	Human GH, Prl, and PL have considerably less homology of amino acid sequence, in contrast to the striking degree that is observed in other species.
Prolactin (Prl)	22,500	1	198	0	
Placental lactogen (PL)	22,300	1	191	0	
<i>Glycoprotein Hormones</i>					
Luteinizing hormone (LH)	29,400	2	α -92 β -115	23%	Glycoproteins with nonidentical subunits (α and β); biological specificity is in β subunit. The amino acid sequences of the α subunits of LH, FSH, TSH, and CG are identical. Although carbohydrate sequences are incomplete, data suggest heterogeneity, even within each hormone.
Follicle-stimulating hormone (FSH)	32,600	2	α -92 β -115	28%	
Chorionic gonadotropin (CG)	38,600	2	α -92 β -145	33%	
Thyroid-stimulating hormone (TSH)	30,500	2	α -92 β -112	22%	
<i>POMC-Derived Hormones*</i>					
Corticotropin (ACTH)	4500	1	39	0	This group of peptides is derived from a common precursor, pro-opiomelanocortin (POMC). Group shares a common heptapeptide: Met-Glu-His-Phe-Arg-Trp-Gly. ACTH (1-13)= α -MSH β -LPH (1-58)= γ -LPH β -LPH (41-58)= β -MSH β -LPH (61-91)= β -Endorphin β -LPH (61-65)=Met-Enkephalin
α -Melanocyte-stimulating hormone (α -MSH)	1650	1	13	0	
β -Melanocyte-stimulating hormone (β -MSH)	2100	1	18	0	
β -Lipotropin (β -LPH)	9500	1	91	0	
γ -Lipotropin (γ -LPH)	5800	1	58	0	

* Discussed in further detail in Chapter 59.

GROWTH HORMONE

Human growth hormone is encoded for by one gene of a five-gene cluster located in the long arm of chromosome 17. The other four genes encode for two different variants of placental lactogen or a growth hormone variant expressed in the placenta.

The growth hormone that is secreted from the pituitary *in vivo* or by pituitary cells maintained in culture is a heterogeneous mixture of peptides that can be distinguished on the basis of size or charge (Bauman, 1991). The principal form of growth hormone is a single polypep-

tide chain of 191-amino-acid residues with a molecular mass of 22 kDa. This polypeptide has two disulfide bonds and is not glycosylated. A smaller form of growth hormone with a molecular mass of 20 kDa also is secreted and accounts for 5% to 10% of the growth hormone present in the pituitary or in the circulation. This form of growth hormone arises by alternative splicing of the growth hormone mRNA and differs from the 22-kDa form by deletion of residues 32 to 46. Its biological potency is the same as that of the 22-kDa form. Additional forms of growth hormone that are larger or smaller than the 22-kDa molecule also have been shown to occur in pituitary cul-

tures or in serum. Their physiological significance is unclear. The placenta also produces an additional 22-kDa growth hormone variant that is distinguishable from the pituitary product.

Secretion

Growth hormone is the most abundant of the anterior pituitary hormones. It is synthesized and secreted by somatotropes, which account for about 50% of the hormone-secreting cells of the anterior pituitary.

The amount of growth hormone secreted during a 24-hour period is high in children, reaches maximal levels during adolescence, and then decreases to its lowest levels during adulthood. Growth hormone secretion is pulsatile and occurs in discrete but irregular bursts. Between these secretory pulses, the concentration of circulating growth hormone falls to undetectable levels. The amplitude of the secretory bursts is maximal at night, and the most consistent period of growth hormone secretion occurs shortly after the onset of deep sleep. For these reasons, measurements of plasma concentrations of growth hormone during the day or over short periods of time are of little value in the diagnosis of growth hormone deficiency. Instead, measurements are done during a 24-hour period or following acute stimulation of release (*see below*).

Somatotropes have spontaneous intracellular Ca^{2+} oscillations that are believed to be responsible for the pulsatile release of growth hormone (Holl *et al.*, 1988). This pulsatile release is regulated by GHRH, which stimulates growth hormone release, and by somatostatin, which inhibits growth hormone release (Figure 55-1). These factors bind to their cognate receptors in the somatotropes and exert their effects through the activation of G proteins, leading to an increase (GHRH) or decrease (somatostatin) in cyclic AMP accumulation and intracellular Ca^{2+} . Several neurotransmitters, drugs, metabolites, and other stimuli also affect growth hormone secretion by acting on the hypothalamus and influencing the secretion of GHRH and somatostatin. For example, dopamine, 5-hydroxytryptamine, and α -adrenergic agonists stimulate growth hormone release, whereas β -adrenergic agonists, free fatty acids, insulin-like growth factor-1 (*see below*), and growth hormone itself inhibit growth hormone release. Plasma glucose also is a powerful modulator of growth hormone release. Therefore, the hypoglycemia that results as a consequence of insulin administration or from other causes evokes a rapid rise in growth hormone secretion. Likewise, exercise, stress, emotional excitement, and ingestion of protein-rich meals are stimuli for enhanced secretion of growth hormone.

These observations form the basis of several provocative tests that can be used to assess the capacity of the pituitary to secrete growth hormone (Thorner *et al.*, 1992). These include an infusion of arginine, the administration of insulin to induce hypoglycemia, or the administration of levodopa (a dopamine precursor). All of these result in a peak of growth hormone release within 45 to 90 minutes, but the arginine infusion is considered to be the safest test. If excessive release of growth hormone is suspected, a suppression test also can be performed by inducing hyperglycemia (*i.e.*, a glucose tolerance test). Although deficiencies in growth hormone release can be detected easily using these tests, they cannot distinguish whether the lesion exists at the level of the hypothalamus or at the level of the pituitary. This can be done only by using GHRH, as described later in this chapter.

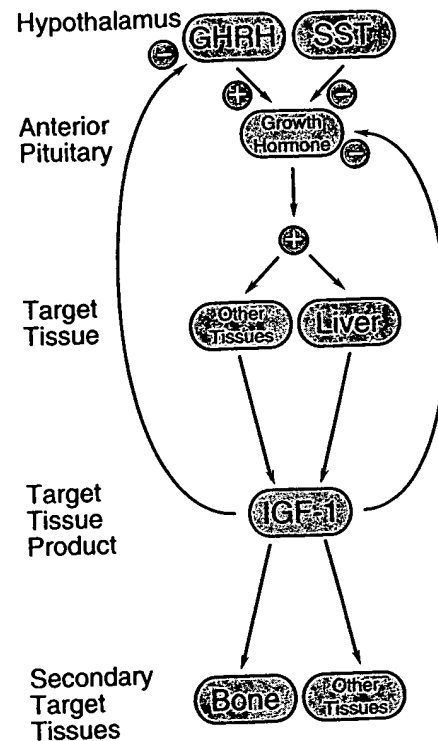


Figure 55-1. Growth hormone secretion and actions.

Two hypothalamic factors, growth hormone-releasing hormone (GHRH) and somatostatin (SST) stimulate or inhibit the release of growth hormone (GH) from the pituitary, respectively. Insulin-like growth factor-1 (IGF-1), a product of GH action on peripheral tissues, causes negative feedback inhibition of GH release by acting at the hypothalamus and the pituitary. The actions of GH can be direct (*see Target tissue*) or indirect and mediated by IGF-1 (*see Secondary target tissues*).

Molecular and Cellular Bases of Growth Hormone Action

All of the effects of growth hormone are the ultimate result of its binding to a specific cell surface receptor which is widely distributed throughout the body. The mature growth hormone receptor is a transmembrane glycoprotein of 620-amino-acid residues. It contains a large N-terminal extracellular domain (about 250 amino acid residues), which is responsible for the binding of the hormone, followed by a single membrane-spanning domain, and a C-terminal cytoplasmic domain of about 350-amino-acid residues (Leung *et al.*, 1987). In human beings, the extracellular domain of the growth hormone receptor can be cleaved by proteases to generate a circulating growth hormone-binding protein with a molecular mass of about 60 kDa. The physiological significance of this circulating growth hormone-binding protein is unknown.

As expected from the structural similarities of growth hormone and prolactin (*see above*), their respective receptors are homologous in amino acid sequence and overall structural organization. The extracellular domains of the growth hormone and prolactin receptors also show amino acid sequence homology to a growing family of receptors, including those of several of the interleukins, interferon, erythropoietin, and macrophage colony-stimulating factor (Kelly *et al.*, 1991; Mathews, 1991).

The three-dimensional structure of the complex formed by growth hormone and the extracellular domain of its receptor has been elucidated (de Vos *et al.*, 1992). The complex consists of one molecule of hormone bound to two molecules of receptor. The sites on the hormone that interact with the two molecules of receptor are different, but the sites on each of the two receptors that interact with the hormone are identical. The signal transduction mechanisms utilized by the growth hormone receptor are not yet fully understood but appear to involve dimerization of the receptor (de Vos *et al.*, 1992). Recent evidence shows that, in spite of the absence of intrinsic tyrosine kinase activity in the growth hormone receptor, the binding of the hormone leads to an increase in the phosphorylation of intracellular proteins on tyrosine residues. These initial phosphorylation events are mediated by certain cytoplasmic protein tyrosine kinases that physically associate with the ligand-bound growth hormone receptor and become activated as a consequence of this association (Campbell *et al.*, 1993).

Although growth hormone has direct effects on lipid and carbohydrate metabolism (*see below*), its anabolic and growth-promoting effects are mediated indirectly by other hormones, collectively known as *somatomedins* or *insulin-like growth factors* (IGFs) (Salmon and Daughaday, 1957). There are two IGFs, IGF-1 and IGF-2, which share homology with each other and with insulin and have insulin-like effects.

IGF-2 has more insulin-like activity than does IGF-1, but IGF-1 is more growth hormone-dependent and more potent as a growth factor than IGF-2 (Daughaday and Rotwein, 1989). IGF-1 appears to function as the principal mediator of the action of growth hormone. Thus, administration of IGF-1 to hypophysectomized rats restores growth; enhances sulfate incorporation into proteoglycans; increases the synthesis of protein, RNA, and DNA; promotes the transport of amino acids and glucose into muscle; increases lipogenesis in adipose tissue; and increases renal plasma flow and glomerular filtration rate (Froesch *et al.*, 1985). Low plasma concentrations of IGF-1 are correlated with dwarfism in human beings (African pygmies) and animals (toy poodles). The IGF-1 receptor is structurally related to the insulin receptor (*see Chapter 60*) and has intrinsic tyrosine kinase activity, which ultimately is responsible for mediating the hormonal signal (Czech, 1989; Ullrich *et al.*, 1986). IGF-1 receptors are present in all tissues studied thus far, in addition to binding IGF-1,

these receptors also can bind insulin and IGF-2. Insulin receptors also are capable of binding IGF-1 and IGF-2, whereas the IGF-2 receptor does not bind insulin but can bind IGF-1.

Although many tissues can synthesize IGF-1 and IGF-2, the liver is considered to be the major source of circulating IGF-1 (Figure 55-1). The synthesis and secretion of IGFs in extrahepatic tissues also are growth hormone-dependent, but the IGFs so produced are believed to act locally as paracrine modulators. The circulating IGFs are bound to a family of binding proteins that serve as transport proteins but also modulate their actions on target tissues (Rosenfeld *et al.*, 1990).

Physiological Effects of Growth Hormone

As indicated above, the physiological effects of growth hormone can be classified as direct or indirect. *Direct effects* include the stimulation of the production of IGFs in the liver and other tissues, stimulation of triglyceride hydrolysis in adipose tissue, and stimulation of hepatic glucose output. These effects are potentiated by glucocorticoids and oppose the effects of insulin (and IGFs) on fat and carbohydrate metabolism (Davidson, 1987). The anabolic and growth-promoting effects of growth hormone are indirect effects mediated by IGF-1. IGF-1 is directly responsible for chondrogenesis, skeletal growth, and the growth of soft tissues. The *indirect effects* of growth hormone are insulin-like (Davidson, 1987) and, in contrast to the direct effects (*see above*), are inhibited by glucocorticoids.

In most tissues, growth hormone acts, indirectly through IGF-1, by increasing cell number rather than cell size. Growth responses to administration of growth hormone have been studied in rats and in human hypopituitary dwarfs. It is clear from these studies that, with the possible exception of the brain and the eyes, most organs and tissues respond to the hormone with an increase in size. The growth response to growth hormone also is associated with a positive nitrogen balance, but this does not persist during prolonged treatment. Growth hormone also increases the transport of amino acids and protein synthesis. This diversion of amino acids into anabolic pathways appears to be responsible for the decrease in blood urea detected in human beings treated with growth hormone. In addition to nitrogen, growth hormone promotes the accretion of other tissue constituents such as Ca^{2+} , Mg^{2+} , K^+ , Na^+ , and phosphate. The overall effects of growth hormone administration on carbohydrate and lipid metabolism are complex. In general, administration of the hormone for several hours leads to metabolic effects that are opposite to those of insulin: increased hepatic glucose output, decreased glucose utilization, and increased lipolysis. Growth

hormone also induces insulin resistance by blocking the actions of receptor-bound insulin. Thus, the net result of the metabolic actions of growth hormone is to shift the source of fuel from carbohydrates to fats. These effects explain why excessive amounts of growth hormone may lead to a diabetic state.

Agents Used in the Treatment of Syndromes of Growth Hormone Deficiency

Growth Hormone. Growth hormone is approved for replacement therapy in growth hormone-deficient children. The preparations of human growth hormone available in the United States are produced by recombinant DNA technology. *Somatropin, recombinant* (HUMATROPE) has an amino acid sequence identical to that of the hormone isolated from human pituitaries. *Somatrem* (PROTROPIN) is a growth hormone analog with an amino acid sequence identical to that of the hormone isolated from human pituitaries, but with an additional methionine residue introduced as the amino-terminal amino acid. Both preparations are equally effective, but somatrem is more antigenic.

Growth hormone can be administered by intramuscular or subcutaneous injection with equal effectiveness. Subcutaneous administration is preferred, because it facilitates self-administration. Maximal plasma concentrations of growth hormone are achieved 2 to 6 hours after injection. About 20% of the circulating hormone is bound to the growth hormone-binding protein mentioned above. Growth hormone is cleared with a half-life of 20 to 30 minutes. Peak plasma concentrations of IGF-1 are apparent about 20 hours after growth hormone injection. Because of this slow induction and clearance of IGF-1, the effects of growth hormone far outlast its survival in the circulation. Growth hormone is degraded in the liver, kidney, and other tissues, and little is excreted in the urine (Bennet and McMartin, 1979).

The goal of growth hormone treatment in growth hormone-deficient children is to promote normal growth rates. Prior to 1985, when recombinant growth hormone became available, growth hormone therapy usually was reserved for children with severe deficiency of the hormone; decisions about whom to treat and how were governed largely by the supply of hormone. The supply is no longer an issue.

The majority of children with growth hormone deficiency respond well to treatment with the hormone; their rate of growth increases over years of treatment until epiphyseal fusion (Frasier, 1983; Jørgensen, 1991). Usually, the rate of growth is greatest during the first year of treatment and then decreases with longer times of therapy. With current treatment regimens, the growth rate may double during the first year. The growth response is a function of the dose given.

The usual treatment regimen is 0.025 to 0.05 mg per kg body weight every other day or three times per week by intramuscular or subcutaneous injection, although daily injections produce slightly better responses without increasing the incidence of side effects. Adolescents do not respond as well as do younger children; obese children respond better than do thin children; and severely growth hormone-deficient children respond better than do those with partial deficiencies of the hormone. Treatment should be continued throughout childhood, and administration of the appropriate gonadal steroids (see Chapters 57 and 58) to prepubertal boys or girls may be needed to elicit sexual maturation and improve the growth response to growth hormone. Gonadal steroids also may need to be given at the age of puberty to promote normal sexual development (Underwood and Van Wyk, 1992).

Pain and discomfort from growth hormone injections are minimal, but subcutaneous injections may lead to local lipatrophy (Frasier, 1983). Antibodies to growth hormone may form during treatment, a phenomenon more pronounced with somatrem than with somatropin. Antibodies to growth hormone are elicited in 30% to 40% and 7% to 20% of children treated with somatrem and somatropin, respectively (Jørgensen, 1991; Marshak and Liu, 1988). Resistance to treatment, however, is rare and frequently can be overcome by increasing the dose of hormone.

In many cases, growth hormone deficiency is associated with a generalized hypopituitarism. When this is the case, replacement therapy with other hormones (such as thyroid hormone and glucocorticoids) also is needed and must be initiated before starting growth hormone therapy. Because of the interactions among growth hormone, glucocorticoids, and insulin (see above and Chapters 59 and 60), care must be taken in the administration of glucocorticoids to children undergoing growth hormone treatment. Likewise, patients receiving growth hormone should be checked frequently for symptoms of diabetes mellitus.

Because of its anabolic effects, growth hormone is under investigation as an adjunct in the treatment of several catabolic conditions such as burn injuries, surgery, and malabsorption. The positive effects of growth hormone on Ca^{2+} retention and on osteogenesis also may be of use in the treatment of osteoporosis and nonhealing fractures.

The availability of large quantities of recombinant growth hormone has allowed its evaluation in other physiological or pathophysiological conditions. Growth hormone administration now has been shown to be effective in accelerating the growth rate of children with constitutional growth delay (growth retardation with delayed puberty) and of short children without growth hormone deficiency. Ethical and other medical considerations that should influence the decision for growth hormone administration to these subjects are discussed in detail elsewhere (Lantos *et al.*, 1989; Underwood and Van Wyk, 1992). In addition to its questionable use in "enhancing" build or height in normal children, growth hormone also has a great potential for misuse in adults. Adult athletes may seek growth hormone to increase muscle mass and decrease body fat in a manner that is undetectable by current drug testing programs. Although these metabolic effects of growth hormone are seen in situations of nutritional limitation, its effects on well-fed athletes whose endogenous production of growth hormone may be high because of exercise are unknown (Underwood, 1984).

IGF-1. Laron-type dwarfism is a rare inheritable disease characterized by the presence of normal or elevated levels of biologically active growth hormone, reduced levels of circulating IGFs, a normal or elevated growth

hormone response to provocative testing, and little or no IGF-1 response to growth hormone injections (Laron *et al.*, 1966). This syndrome is due to mutations of the growth hormone receptor gene that either prevent growth hormone binding or cause other defects in the receptor that prevent growth hormone from eliciting its biological effects (Rosenfeld *et al.*, 1994). These patients obviously cannot be treated with growth hormone, because they do not respond to it. On the other hand, initial trials in which Laron-type dwarfs have been treated with recombinant human IGF-1 are encouraging (Rosenfeld *et al.*, 1994), and this form of treatment may be approved in the future.

Because many of the actions of growth hormone are mediated by IGF-1 (*see above*), this hormone may prove to be as effective as growth hormone. Indeed, like recombinant human growth hormone, recombinant human IGF-1 induces a net anabolic effect on bone mineral. Thus, the use of IGF-1 in the treatment of osteoporosis also is undergoing clinical study.

Drugs Used in the Treatment of Syndromes of Growth Hormone Excess

Dopamine Agonists. Excessive secretion of growth hormone, GHRH, or IGFs causes acromegaly in adults or gigantism, if the excessive secretion starts before epiphyseal closure. Somatotrope adenomas (*i.e.*, growth hormone-producing adenomas) account for over 80% of the cases of acromegaly. The prevalence and annual incidence of this disorder have been estimated to be 50 to 70 cases per million and 3 to 4 cases per million, respectively (Klibanski and Zervas, 1991; Melmed, 1990). The treatment of choice for patients with somatotrope adenomas is irradiation or surgical removal of the tumor. Drug therapy is indicated for patients not cured by surgery and those with recurring problems. Growth hormone secretion by adenomas can be suppressed with orally active dopaminergic agonists such as *bromocriptine* (PARLODEL) (Melmed, 1990). The effect of dopaminergic agonists on growth hormone secretion by pituitary adenomas is paradoxical, as these agents actually increase growth hormone secretion in the normal pituitary. This paradox may reflect the clonal expansion in these adenomas of stem cells that express the inhibitory dopaminergic regulation of secretion characteristic of lactotropes (*see below*) rather than of somatotropes. The pharmacology of bromocriptine is more fully discussed below.

Somatostatin and Analogs. Growth hormone-secreting adenomas retain their sensitivity to somatostatin, and long acting somatostatin analogs have proven useful in reducing growth hormone release by these tumors. Although not approved for the treatment of acromegaly, *octreotide* (SANDOSTATIN) is believed by many to be a more effective drug than bromocriptine in the treatment of acromegaly. A major disadvantage, however, is that it requires three daily subcutaneous injections to effectively inhibit growth hormone release during a 24-hour period (Melmed, 1990). Octreotide is discussed more fully below.

GROWTH HORMONE-RELEASING HORMONE

Human GHRH is a single polypeptide chain of 44 amino acid residues derived from a 108 amino acid residue precursor. Synthetic peptides that contain only the first 29 amino acids are fully efficacious and are nearly as potent as the full-length GHRH. GHRH is a member of the glucagon-secretin peptide family, but these latter hormones do not have GHRH activity.

Biological Actions

The binding of GHRH to its cognate receptor (a member of the G protein-coupled receptor family, *see Chapter 2*) results in the activation of adenylyl cyclase and increased cyclic AMP levels in somatotropes. Cytosolic Ca^{2+} also is increased by GHRH. These events ultimately result in a stimulation of the synthesis, *via* increased transcription of the GHRH gene, and release of GHRH. When injected into human beings, the effects of GHRH are remarkably specific in stimulating growth hormone release; there is little or no effect on other pituitary hormones.

Pharmacology of GHRH

GHRH is used mainly as a diagnostic agent. The measurement of endogenous growth hormone release following an injection of GHRH allows physicians to determine if growth hormone deficiency is due to a hypothalamic or a pituitary defect. As many as 40% to 80% of growth hormone-deficient children respond to GHRH, suggesting that the defect in many of these children is, in fact, hypothalamic. Treatment of these children with GHRH increases their rate of growth (Gelato and Merriam, 1986).